Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies

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Summary

In order to establish a safe and reliable treatment for human immunodeficiency virus (HIV)-associated scabies, we have treated 60 episodes of scabies in this setting, occurring in 39 patients, with one of the following regimens: (i) topical treatment with benzyl benzoate solution; (ii) single-dose oral treatment with ivermectin alone; and (iii) combination therapy with benzyl benzoate solution and oral ivermectin, employing the same regimens as single-agent therapy. Patients were stratified according to the severity score of the disease and the outcome (eradication, relapse, failure). We found that both benzyl benzoate and ivermectin alone were quite effective in mild to moderate scabies, but they were both associated with an unacceptable rate of relapse and failure in severe or crusted scabies. In contrast, combined treatment produced an optimal rate of success, without significant treatment-related side-effects. Therefore, we consider that combination treatment with benzyl benzoate solution and oral ivermectin is preferable to single-agent therapy in crusted scabies occurring in HIV/acquired immune deficiency syndrome patients.

Key words: acquired immune deficiency syndrome, human immunodeficiency virus, ivermectin, scabies, topical treatments

Severe scabies, sometimes of the crusted type, may occur in patients infected with human immunodeficiency virus (HIV). These patients, like others with conditions leading to moderate to severe immune impairment (e.g. cancer patients, transplant recipients), are often unable to mount an adequate immune response, have diffuse and atypical rashes, and are considerably more infectious than patients with classical scabies. They may be responsible for outbreaks of scabies in hospitals and other care facilities.

Crusted or Norwegian scabies is an unusual variant of scabies, first described in a group of leprosy patients in Norway, in which the mite population is very numerous, and which is characterized by extensive hyperkeratotic, scaling and crusted lesions.

Treatment failure is frequently encountered when topical scabicides are used to treat crusted scabies, probably because of poor penetration into the crusted areas. Ivermectin is a chemically modified avermectin, a class of antiparasitic agents produced by the actinomycete Streptomyces avermitilis. It is widely used as an antiparasitic drug in veterinary practice and has been used in humans for treating onchocerciasis and Strongyloides infections. There have been several reports of the successful use of ivermectin in human scabies, including the crusted type, either alone or in combination with topical treatments, and the combination therapy seems to be more effective than single drug use, especially in severe cases. Moreover, the prophylactic use of ivermectin in close contacts is considered reliable and effective. In order to establish the most effective protocol for management of HIV-associated scabies, we performed an open study of 60 episodes of scabies, occurring in 39 HIV-positive patients attending our institution during an epidemic outbreak, who were given three different treatment regimens: (i) topical therapy with 15% benzyl benzoate solution (BBS); (ii) systemic therapy with ivermectin alone, or (iii) combination therapy with oral ivermectin and BBS.

Patients and methods

We performed a retrospective analysis of all records concerning HIV-positive patients suffering from scabies...
who were admitted to our institution during an epidemic outbreak which occurred between January 1995 and December 1996. The diagnosis of scabies was either clinical or microbiological, i.e. evidence of mites, eggs or faeces in skin scrapings. Patients who had received scabicide treatment within 2 weeks prior to hospital admission were excluded from the study. Epidemiological and clinicoimmunological data (CD3+ and CD4+ cell count and stage of HIV infection) were recorded for each admission, and a prior-to-treatment grading of the severity of each episode was performed according to Meinking et al.3 classifying scabies severity as mild (< 10 lesions), moderate (11–50 lesions), severe (> 50 lesions) and crusted. For every episode recorded, each patient was assessed for 5 days after treatment, and underwent clinical and microbiological re-evaluation at 1, 2 and 4 weeks thereafter. With regard to treatment outcome, we considered: (i) a complete clinical response as both resolution of itching and either dermatological or microbiological cure; (ii) a relapse as the recurrence of infestation within 2 months of a negative skin scraping; (iii) treatment failure as persistent microbiological evidence of infestation within 4 weeks of treatment.

Treatment regimens, initiated by individual physicians, differed during the epidemic and were based on the availability of a limited amount of ivermectin at the time. We subsequently decided to treat any new case, or retreat persistent cases with a schedule containing a single dose of ivermectin. Thus, treatment regimens became the following: (i) topical therapy with 15% BBS (one application twice daily for 3 days); (ii) systemic therapy with oral ivermectin alone (single dose of 200 µg kg⁻¹); and (iii) combined therapy with oral ivermectin and topical treatment, using the same regimens as those employed in single-agent therapy. We also treated 78 close contacts of patients, who were considered to be particularly at risk of infection, with a single dose of oral ivermectin (direct observation of therapy, 100% adherence), and encountered only three cases of proven transmission of scabies (4%).

The analysis of data was then performed stratifying the cases into three treatment arms; each arm was then considered with regard to pretreatment severity score and outcome (i.e. eradication, relapse or failure).

**Results**

Thirty-nine HIV-positive patients (29 men and 10 women) entered the study. Twenty-five patients (64%) had severe immunological impairment (CD4+ < 100 mm⁻³); five (13%) had a CD4+ cell count between 101 and 200 mm⁻³, four (10%) between 201 and 500 mm⁻³, and five (13%) > 500 mm⁻³. At the time of initial presentation, the disease was scored as mild in four cases, moderate in 12, severe in 15 and crusted in eight.

BBS was employed as first-line therapy in 19 patients, ivermectin alone in 16 and combination therapy in four. Overall, 60 treatment courses were given, including retreatments required either for relapses (10 cases) or for failures (11 cases): BBS in 22 episodes, ivermectin alone in 21 and the combined treatment in 17. Correlations between severity score at initial presentation, first treatment option and response are summarized in Table 1. Similar results were obtained when evaluating all the treatment courses: BBS treatment was associated with complete response in 10 of 22 cases (45%), relapse in eight of 22 (36%) and failure in four of 22 (18%). Ivermectin alone

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**Table 1. Relationship between severity score, first treatment and response to therapy in 39 patients**

<table>
<thead>
<tr>
<th></th>
<th>BBS</th>
<th>I</th>
<th>BBS + I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2/2</td>
<td>2/2</td>
<td></td>
<td>4/4</td>
</tr>
<tr>
<td>Moderate</td>
<td>6/7</td>
<td>5/5</td>
<td></td>
<td>11/12</td>
</tr>
<tr>
<td>Severe</td>
<td>1/7</td>
<td>3/8</td>
<td></td>
<td>4/15</td>
</tr>
<tr>
<td>Crusted</td>
<td>0/3</td>
<td>0/1</td>
<td>4/4</td>
<td>4/8</td>
</tr>
<tr>
<td>Total</td>
<td>9/19</td>
<td>10/16</td>
<td>4/4</td>
<td>23/39</td>
</tr>
</tbody>
</table>

BBS, benzyl benzoate solution; I, ivermectin.
produced complete response in 12 of 21 cases (57%), relapse in seven of 21 (33%) and failure in two of 21 (10%). Combination therapy was successful in 17 of 17 cases (100%) (see Fig. 1).

Discussion

Scabies presents a challenge to physicians, both in their choice of the most effective treatment and in the control of community-based epidemics. These issues are of even greater concern when dealing with severe or crusted scabies in immunosuppressed individuals such as those suffering from HIV infection/acquired immune deficiency syndrome (AIDS).

Until recently, 1% lindane (gamma-benzene hexachloride) was a commonly used scabicide, but concerns about adverse effects and the possible development of resistance have contributed to declining usage. Permethrin 5% cream is now considered by many to be the best topical treatment presently available, but BBS, which is the only topical treatment currently available in our hospital, is a long-established and effective alternative. However, although topical agents are effective in the management of classical scabies, they are less successful in dealing with severe/crusted scabies. In addition, an increasing number of reported failures of topical therapy has led to suggestions of the development of drug resistance, possibly related to the over-use of such preparations.

Hence, the high incidence of severe and crusted scabies among patients with HIV infection/AIDS, and the frequent spread of scabies to close contacts or within communities in these circumstances, present a challenge to find a more effective treatment regimen.

Ivermectin is an anthelmintic used widely in veterinary medicine for nematode, insect and acarine parasites, including Sarcoptes scabiei. It has also been used world-wide in humans for treating onchocerciasis, strongyloidiasis and other parasitic infestations. There are several reports of its efficacy in human scabies, including crusted scabies, which has selective activity against parasites, with almost no adverse effects in mammals. An increase in the death rate among residents in a long-term care facility after the use of ivermectin has remained unconfirmed.

In our experience, the initial use of a topical scabicide alone, although successful in some patients, was of limited efficacy in crusted scabies and unreliable in treating close contacts when asymptomatic. We then combined ivermectin and BBS in the treatment of HIV/AIDS patients, who were admitted to hospital for a short time in order to avoid further transmission, and we gave a single oral dose of ivermectin prophylactically to every contact of the patients. Some nursing staff/carers, who were concerned about potential infection, were also given prophylactic ivermectin. No significant adverse effects were encountered during treatment. There were very few cases of transmission among contacts (three of 78), or new cases among nursing staff who cared for these patients.

Our experience has been that treatment of HIV/AIDS-associated scabies with a single dose of oral ivermectin alone was effective only in cases we classified as mild to moderate, and that there were several relapses and treatment failures in crusted scabies. However, combination therapy with ivermectin and BBS was extremely effective. We therefore consider that combined treatment with ivermectin and BBS is a useful regimen to employ in the management of scabies, particularly the crusted variety, in patients with HIV infection/AIDS.

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